IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#17

In re:	U.S. Patent No. 4,376,858	:	
Patentee:	Norman L. Colbry	:	**Box: Patent Term Extension**
Issue Date:	March 15, 1983	:	

PETITION UNDER 37 C.F.R §1.182 REQUESTING SUSPENSION OF PUBLICATION OF THE CERTIFICATE OF EXTENSION FOR U.S. PATENT NO. 4,376,858

Box Patent Term Extension
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231
Attn: Special Program Law Office

Sir:

In response to the Notice of Final Determination ("NOFD") dated August 4, 1995, and a telephone conversation August 29, 1995, with Gerald A. Dost, Senior Legal Advisor, Special Program Law Office, U.S. Patent & Trademark Office ("PTO"), Applicant, Warner-Lambert Company, hereby petitions the Commissioner, under 37 C.F.R. §1.182, to suspend publication of the Certificate of Extension for U.S. Patent No. 4,376,858 ("'858 patent"), which is scheduled to be issued pursuant to the aforementioned NOFD, until a decision is reached on Applicant's concurrently filed petition to the Food and Drug Administration ("FDA") (copy attached) and request for reconsideration to the PTO.

The following information is submitted in support of Applicant's petition:

1. Applicant submits that the FDA's calculation of the regulatory review period for Neutrexin™, which is covered by the '858 patent, is incorrect. Thus,

Applicant has petitioned the FDA for reconsideration of the regulatory review period determination (see attached copy).

2. Additionally, in order to comply with the NOFD and pursuant to 37 C.F.R. §1.750, Applicant submits the attached "Request for Reconsideration of Final Determination of the Length of Extension of the Term of U.S. Patent No. 4,376,858".

The Commissioner is hereby authorized to charge the amount of $130.00, in payment of the fee set forth in 37 C.F.R. §1.17(h) to Deposit Account **23-0450**, as well as any additional fees associated with this petition, or credit any overpayment to said Deposit account. A duplicate copy of this petition is enclosed.

In view of the above remarks, Applicant respectfully requests that the Commissioner grant the subject petition.

WARNER-LAMBERT COMPANY

By: _____

Francis J. Tinney
Reg. No. 38,069
Assistant Secretary
WARNER-LAMBERT COMPANY
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7295

Date: September 1, 1995

FT1S3883.95

Attachment

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 4,376,858	:	
Patentee:	Norman L. Colbry	:	**Box: Patent Term Extension**
Issue Date:	March 15, 1983	:	

REQUEST FOR RECONSIDERATION OF FINAL DETERMINATION OF THE LENGTH OF EXTENSION OF THE TERM OF U.S. PATENT NO. 4,376,858

UNDER 37 C.F.R. §1.750

Box Patent Term Extension
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Notice of Final Determination ("NOFD") dated August 4, 1995, Applicant, Warner-Lambert Company, hereby requests reconsideration of the Final Determination of the Length of Extension of the Term of United States Patent No. 4,376,858 ("'858 patent") under 37 C.F.R. §1.750.

The NOFD states, at page 1, lines 14-15, "A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice" (emphasis added). A copy of this notice is attached as Exhibit 1*.

* *Material not relevant to support Applicant's Request for Reconsideration has been deleted from the Exhibits.*

Thus, Applicant submits that the subject request for reconsideration is proper and in accord with 37 C.F.R. §1.750.

The following information is submitted in support of Applicant's request:

I. **PERIOD OF EXTENSION**

On February 8, 1994, Applicant submitted an application for extension of the term of the '858 patent covering Neutrexin™ which was approved for marketing December 17, 1993. Applicant requested 1310 days of term extension. This was based on a testing phase of 1980 days and an approval phase of 320 days for Neutrexin™.

Pursuant to a request from the Patent and Trademark Office ("PTO"), the Food and Drug Administration ("FDA") determined that the testing phase was 1934 days and the approval phase was 317 days (Federal Register Vol. 59, No. 167, August 30, 1994). Based on this, the PTO calculated a term extension of 1284 days for the '858 patent. This calculation is 26 days less than Applicant requested. Applicant submits that the FDA's calculation of both the testing phase and the approval phase is incorrect due to the use of incorrect dates for the date the investigational new drug application became effective ("IND Effective Date") and the date the new drug application was submitted ("NDA Submission Date"). Applicant submits that the IND Effective Date is September 2, 1987 (not October 21, 1987), and the NDA Submission Date is February 1, 1993 (not February 4, 1993, as determined by the FDA).

II. IND EFFECTIVE DATE

(a) IND SUBMISSION

On March 9, 1987, Applicant submitted an IND for trimetrexate glucuronate parenteral (Neutrexin™). A copy of this letter is attached as Exhibit 2 (this is Exhibit 5 of the Request for Extension of Patent Term). The IND was received by the FDA on March 10, 1987, as evidenced by attached Exhibit 3.

(b) CLINICAL HOLD

On March 30, 1987, Applicant received a telephone call from the FDA indicating the IND was on clinical hold. A copy of this telephone contact with the FDA is attached as Exhibit 4.

On June 1, 1987, Applicant received a letter dated May 27, 1987, from the FDA outlining issues regarding the clinical hold and identifying a "promised" dog toxicity study as one of the items responsible for the clinical hold. A copy of this letter is attached as Exhibit 5.

On June 19, 1987, Applicant received a telephone call from the FDA indicating the dog toxicity study protocol had been reviewed and approved by the FDA. A copy of this telephone contact with the FDA is attached as Exhibit 6.

A letter dated July 23, 1987, was sent by Applicant to Dr. Judith Feinberg (NIAD/AIDS) (with copies to FDA participants) regarding a June 17, 1987, meeting with FDA, NCI and NIAID, noting that the clinical hold would be removed pending receipt of a letter to the FDA from Applicant confirming that the dog study was underway (first

paragraph of letter). A copy of this letter is attached as Exhibit 7.

On August 7, 1987, Applicant received a letter dated August 4, 1987, from the FDA summarizing discussions from the June 17, 1987, meeting which indicated the dog toxicity protocol was reviewed and approved on June 19, 1987 (item 1 in letter), and that the IND clinical study could proceed when notification that vascular accesses had been implanted in 24 dogs (Item 4 in letter). A copy of this letter is attached as Exhibit 8.

On October 7, 1987, the FDA forwarded a letter to Dr. Maureen Myers at ATEU indicating that the FDA received notification from Warner-Lambert on August 28, 1987, that vascular access ports had been implanted in 24 dogs (as agreed at the June 17, 1987, meeting) and that dosing in this dog toxicity study would begin on September 8, 1987. A copy of this letter is attached as Exhibit 9.

On September 2, 1987, Applicant received a telephone call from the FDA indicating that the clinical hold had been lifted. A copy of this telephone contact with the FDA is attached as Exhibit 10 (this is Exhibit 6 of the Request for Extension of Patent Term).

On October 26, 1987, Applicant received a letter dated October 21, 1987, from the FDA indicating the Phase III study may proceed but failed to mention the September 2, 1987, telephone notification to Applicant that the clinical hold had been lifted. A copy of this letter is attached as Exhibit 11.

The aforementioned documentation evidences the fact that the clinical hold was lifted on September 2, 1987, not October 21, 1987. As further support, Applicant notes that 21 C.F.R. §312.42(e) which concerns clinical holds and requests for modification states:

> (e) *Resumption of clinical investigations.* If, by the terms of the clinical hold order, resumption of the affected investigation is permitted without prior notification by FDA once a stated correction or modification is made, the investigation may proceed as soon as the correction or modification is made. In all other cases, an investigation may only resume after the Division Director (or the Director's designee) with responsibility for review of the IND has notified the sponsor that the investigation may proceed. In these cases resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfied the agency that the investigation(s) can proceed. Resumption of a study may be authorized by telephone or other means of rapid communication. (Emphasis added)

Applicant submits in accord with 21 C.F.R. §312.42(e) that the telephone contact on September 2, 1987, by Mr. Bona (FDA, CSO) to Dr. T.N.T. Olson (Warner-Lambert) indicating that the clinical hold had been lifted supports the fact that the IND became effective as of that date.

Thus, Applicant submits that the correct number of days in the testing phase calculated using the IND Effective Date of September 2, 1987, is 1980 days.

III. **NDA SUBMISSION DATE**

On February 1, 1993, an NDA was submitted by U.S. Bioscience (marketing entity for Neutrexin™) to the FDA. A copy of the cover letter of February 1, 1993, is attached as

Exhibit 12 (this is Exhibit 7 of the Request for Extension of Patent Term).

On February 8, 1993, U.S. Bioscience received a letter dated February 4, 1993, from the FDA which shows that the date of NDA submission is February 1, 1993. A copy of this letter is attached as Exhibit 13.

Thus, Applicant submits that the correct number of days in the approval phase calculated using the NDA submission date of February 1, 1993, is 320 days.

Therefore, when the above regulatory review periods are used, Applicant submits that the period of extension for the '858 patent should be 1310 days as originally requested (rather than 1284 days suggested by the PTO).

IV. **CONCLUSION**

Applicant respectfully requests reconsideration of the NOFD in view of the previous remarks. Specifically, Applicant requests correction of the FDA determination of the regulatory review period for Neutrexin™. Upon correction and recalculation, the length of the period of

extension of the '858 patent to which Applicant is entitled is 1310 days, not 1284 days.

WARNER-LAMBERT COMPANY

By: _____

Francis J. Tinney
Reg. No. 33,069
Assistant Secretary
WARNER-LAMBERT COMPANY
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
(313) 996-7295

Date: September 1, 1995

FT1S3878.95

Attachments: (Exhibits 1-13)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

AUG - 4 1995

Francis J. Tinney
Patent Department
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48105

Re: Patent Term Extension
Application for
U.S. Patent No. 4,376,858

AUG 11 1995

NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 4,376,858 issued March 15, 1983, which claims the human drug product Neutrexin, is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,284 days.

The period of extension has been calculated using the FDA determination of the length of the regulatory review period published in the Federal Register of August 30, 1994. Under 35 U.S.C. § 156(c):

Period of Extension = 1/2 (Testing Phase) + Approval Phase
= 1/2 (1,934) + 317
= 1,284 days

Since the regulatory review period began after the patent issue date, the entire period has been considered in the above calculation. No determination of lack of due diligence was made.

The limitation of 35 U.S.C. 156(g)(6) and the 14 year exception of 35U.S.C. § 156(c)(3) do not operate to reduce the period of extension determined above.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Commissioner will issue a certificate of extension, under seal, for a period of 1,284 days.

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

U.S. Patent No.:	4,376,858
Granted:	March 15, 1983
Applicant:	Norman L. Colbry
Owner of Record:	Warner-Lambert Company
Title:	2-4- DIAMINO-5-METHYL-6-[(3,4,5-TRIMETHOXYANILINO) METHYL]QUINAZOLINE SALTS
Classification:	544/291
Product Trade Name:	Neutrexin
Term Extended:	1,284 days

Gerald A. Dost

Gerald A. Dost
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

(703) 305-9285

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fisher's Lane, Room 11-44
Rockville, MD 20857

RE: Neutrexin

FDA Docket No.: 94E-0099

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0014
Expiration Date: December 31, 1984

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

NOTE: No drug may be shipped or study initiated unless a complete statement has been received. *(21 CFR 312.1(a)(2)).*

Name of Sponsor Warner-Lambert Company Date MAR 9 1987

Address 2800 Plymouth Road, P.O. Box 1047
Ann Arbor, Michigan 48106 Telephone (313) 996-7428

Name of Investigational Drug Trimetrexate Glucuronate Parenteral

FOR A DRUG:

Food And Drug Administration
Office of New Drug Evaluation *(HFN-106)*
5600 Fishers Lane
Rockville, Maryland 20857

FOR A BIOLOGIC:

Food and Drug Administration
Office of Biologics *(HFN-823)*
8800 Rockville Pike
Bethesda, Maryland 20205

Dear Sir:

The sponsor, Warner-Lambert Company, submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, or each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to under-

take the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed Form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man - only animal and in vitro data are available - with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review board (IRB). The sponsor must give assurance that an IRB that complies with the requirements set forth in Part 56 of this chapter will be responsible for the initial and continuing review and approval of the proposed clinical study. The sponsor must also provide assurance that the investigators will report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and that the investigators will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazard to the human subjects. FDA will regard the signing of the Form FDA-1571 as providing the necessary assurances above.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. A limitation on an exemption does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withhold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, and additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 25.1 of this chapter.

16. A statement that all nonclinical laboratory studies have been, or will be, conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if such studies have not been conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in conducting the study and those required in the regulations.

Very truly yours,

Original signed by

SPONSOR	PER T. N. T. Olson
Warner-Lambert Company	T. N. T. Olson, Ph.D.
	INDICATE AUTHORITY
	Director, Regulatory Liaison and Compliance

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

cc: Dr. J. F. Bender/Dr. A. J. Grillo-Lopez
Regulatory Affairs, MP

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FILE COPY

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Food and Drug Administration
Rockville MD 20857

MAR 13 1987

IND 29,796

Warner-Lambert Co.
Attention: T. N. T. Olson, Ph.D.
2800 Plymouth Rd.
P.O. Box 1047
Ann Arbor, Michigan 48106

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	29,796
Sponsor:	Warner-Lambert Co.
Name of Drug:	Trimetrexate Glucornate Parenteral
Date of Submission:	March 9, 1987
Date of Receipt:	March 10, 1987

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

U.S. GOVERNMENT PRINTING OFFICE-1984-447-553/7406

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call:

Consumer Safety Officer Mr. J. Bona
(301) 443- 6797

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Center for Drugs and Biologics, HFN-815
Attention: DOCUMENT CONTROL ROOM (12B-30)
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228e (5/84)

RECEIVED

MAR 16 1987

REGULATORY LIAISON
AND COMPLIANCE

U.S. GOVERNMENT PRINTING OFFICE: 1984 - 444-900/7357

IND FILE COPY

4

WARNER LAMBERT

Memorandum

Memo to: Trimetrexate Glucuronate Parenteral
Location: IND File (IND 29,796)

Date: MAR 30, 1987

From: John F. Bender, Pharm.D.
Location: Clinical Oncology Research Program

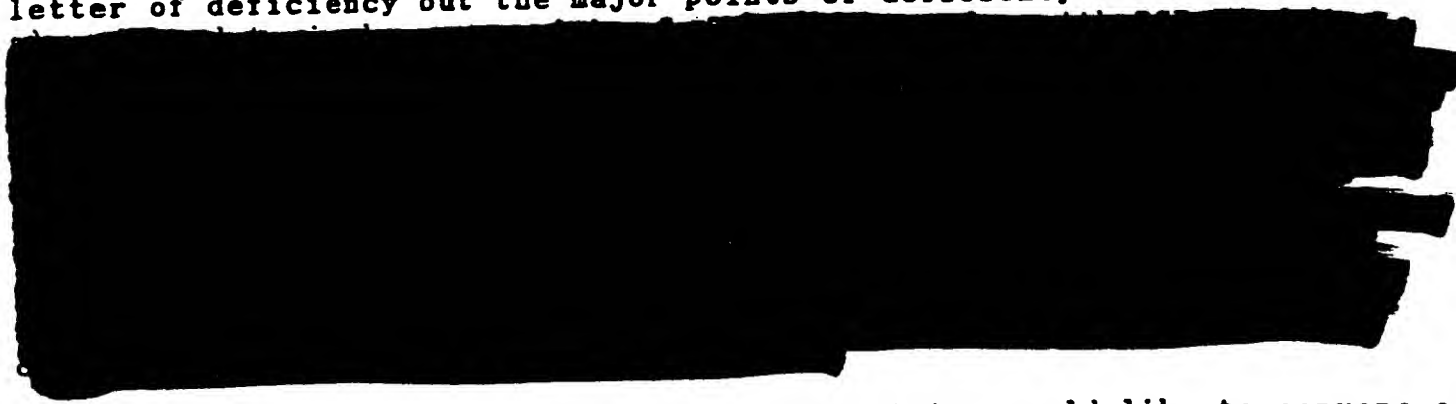
Subject: FDA Clinical Hold on the Phase 3 Trial of CI-898 (Trimetrexate) for the treatment of Pneumocystis carinii pneumonia in AIDS patients.

The IND for the use of trimetrexate in the treatment of AIDS patients with Pneumocystis carinii pneumonia was filed with the FDA on March 9, 1987. It was received by the FDA on March 10, 1987 and the IND number 29,796 was assigned. On March 25, 1987, Mr. Jack Meisenhelder called Mrs. Shortall to suggest a date for an FDA meeting to discuss the IND submission. Points of discussion were to be as follows:

a) Toxicology - Should we proceed with the 5 week leucovorin rescue dog study in view of the human data (56 pts) accumulated by the NIH; if so, at what doses?

b) Orphan Drug NDA - In view the Orphan Drug designation of trimetrexate for the treatment of Pneumocystis carinii pneumonia in AIDS patients, is our proposed study design adequate for an NDA?

On March 27, 1987, Mr. Meisenhelder was informed by Mrs. Shortall that no meeting was presently necessary and to please call Mr. James Bona (FDA Consumer Safety Officer). Mr. Meisenhelder called Mr. Bona who asked that our clinical monitor call and discuss the issue with Dr. Reneta Albrecht (FDA Medical Officer). Several calls were placed to Dr. Albrecht by Dr. Bender on Friday, March 27, 1987 without success. On Monday, March 30, 1987, Dr. Bender received a return call from Dr. Albrecht. Dr. Albrecht stated that the IND is on clinical hold. We will eventually receive a letter of deficiency but the major points of deficiency were:



Once these issues have been resolved, the Division would like to convene a meeting to discuss the Phase 3 study and our proposed NDA submission.

John F. Bender

John F. Bender, Pharm.D.

DEPARTMENT OF H[redacted]TH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FILE COPY

5

IND 29,796

Thomas Olson, Ph.D.
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, Michigan 48106

MAY 27 1987

Dear Dr. Olson:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND) for Trimetrexate (TMTX). Also refer to the meeting held on February 24, 1987, between representatives of the National Cancer Institute and our Division which Dr. John F. Bender from Warner-Lambert attended. In addition, refer to the telephone conversation on March 30, 1987, between Dr. John Bender and Dr. Renata Albrecht.

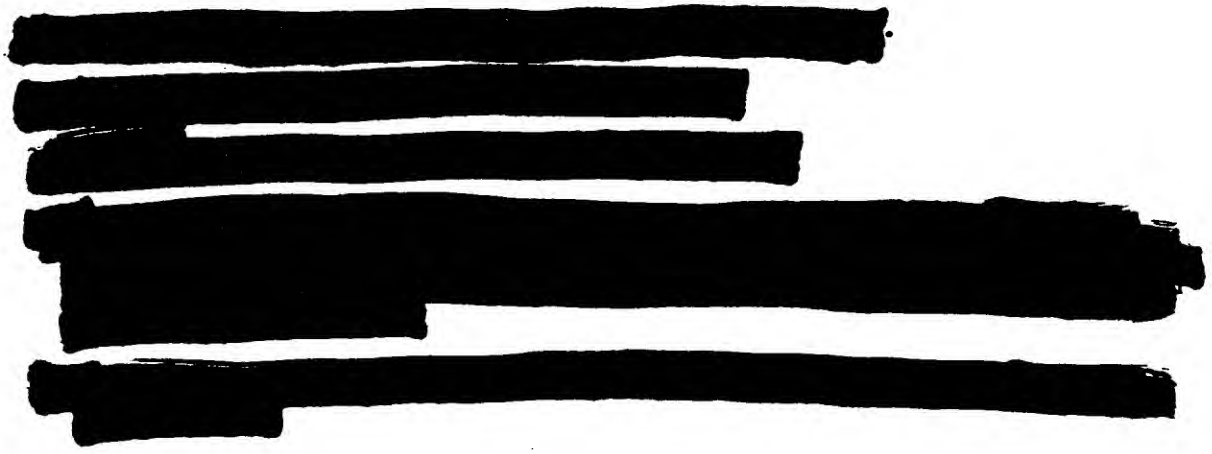
As relayed to Dr. Bender on March 30, 1987, Protocol #898-34 is on clinical hold. The following information should be submitted:

1. The protocol for the five-week dog toxicity study of TMTX with leucovorin. At a meeting held December 26, 1985, between representatives of the NCI and this Division, it was agreed that dog studies would be performed by Warner-Lambert and the duration of treatment and doses of TMTX and leucovorin would exceed those planned for therapeutic administration in any patients.

2. A full report on the Phase I study performed in AIDS patients with TMTX at NCI by Dr. Henry Masur. It should include comprehensive clinical and laboratory results with follow-up data, adverse drug events, and circumstances regarding dose modification.

3. Data from the NCI dose escalation study being conducted by Drs. Masur and Sattler.

Specifically regarding Protocol #898-34, the following recommendations and comments should be addressed:



[redacted]

Furthermore, the NCI dose escalation study of TMTX will not be allowed to proceed beyond the 60 mg/M^2 dose until results from the five-week dog toxicity study are received and reviewed by this Division.

[redacted]

Your submmission of additional data should be in triplicate and identified with IND 29,796.

Sincerely yours,

E. Tabor

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

IND FILE COPY

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WARNER LAMBERT

Memorandum

Memo to: Trimetrexate (CI-898); Pneumocystis, IND 29,796 File
Location:

Date: June 19, 1987

From: G. Clinthorne
Location: NDA Liaison

Subject: FDA Contact

This morning Mr. James Bona, FDA CSO in the Anti-Infective Drug Products Division, called in regard to the 5-week dog study protocol that had been provided to the FDA for review at the June 17, 1987 conference. He informed me that Dr. Norma Browder had reviewed the protocol and wanted us to be advised that the protocol was approved and that we can proceed with the study.

G. Clinthorne

GC/ads

G. Clinthorne

cc: Dr. J. Bender
Dr. F. A. de la Iglesia
Dr. W. W. Downie
Dr. A. J. Grillo
Mr. C. E. Lents
Dr. D. R. Maxwell
Dr. M. McKenna
Mr. J. E. Meisenhelder
Dr. T. N. T. Olson
Dr. D. G. Pegg
Dr. J. A. Weisbach

RECEIVED
JUN 19 1987
IND LIAISON

Warner-Lambert Company
Pharmaceutical Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
313 996-7000

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7

WARNER LAMBERT

July 23, 1987

Judith Feinberg, M.D.
NIAID/AIDS
Westwood Building - Room 753
5333 Westbard Avenue
Bethesda, MD 20816

Dear Judy:

As a result of the FDA meeting June 17, 1987 which you attended, it was agreed that the Clinical Hold on the Phase 3 Study of trimetrexate for the treatment of PCP in AIDS patients would be removed pending receipt of a letter from Warner-Lambert/Parke-Davis confirming that the dog study was underway. In addition, it was agreed with the FDA that the dog study be conducted at 30mg/M2/day x 5 weeks since this would be the Phase 3 clinical dose. The dogs are in Ann Arbor and are being readied for surgery to implant i.v. access ports.

[redacted]

In addition, we have made plans to come to Washington Monday, July 27, 1987 to draw up a "Memo of Agreement" concerning the ATEU conduct of the Phase 3 PCP trial.

[redacted]

[redacted]

Sincerely,

John F. Bender, Pharm.D.

cc: Dr. Albrecht
Dr. Allegra
Dr. Chabner
Dr. Downie
Dr. Grem
Dr. Grillo
Dr. Hoth
Mr. Howard
Dr. Masur
Dr. Myers
Dr. Olson
Dr. Sattler
Dr. Schaumberg
Dr. Shoemaker
Dr. Weisbach

cc: Regulatory Affairs

DEPARTMENT OF H[redacted]TH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 29,796

Travis Olson, Ph.D.
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106

AUG 4 1987

Dear Dr. Olson:

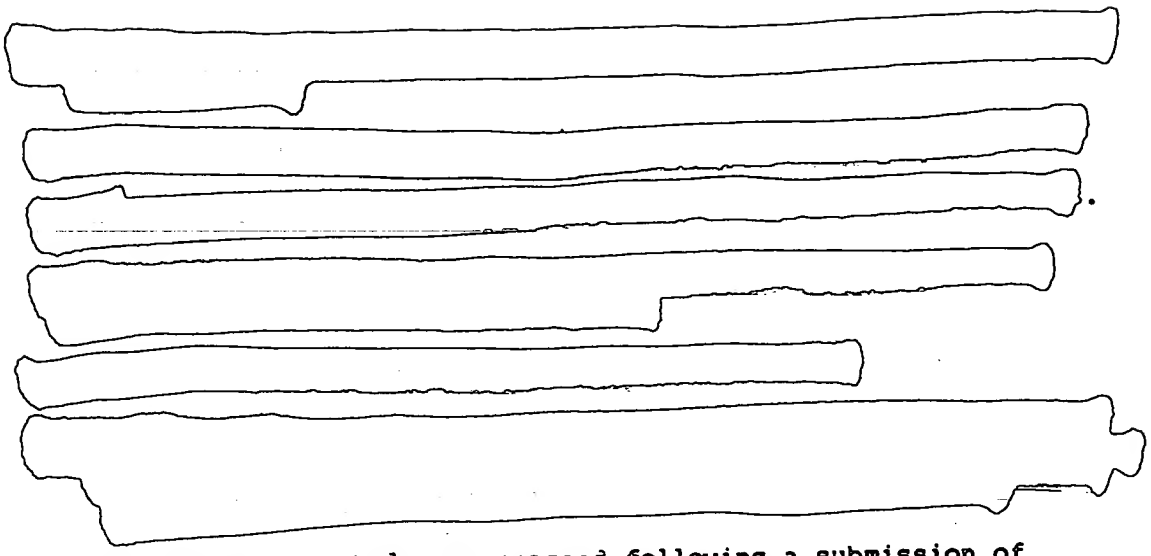
Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND) for Trimetrexate (TMTX). Please also refer to the meeting on June 17, 1987, among representatives from your company, the National Cancer Institute and this Division and refer to the letter from us to you dated May 27, 1987.

The purpose of the meeting was to discuss several issues germane to removing the hold status placed on Phase III studies of TMTX as well as other aspects of drug development. Comments and consensus agreements reached at the meeting are summarized below. In addition, various other topics are also included which due to time restraints were not discussed at the meeting.

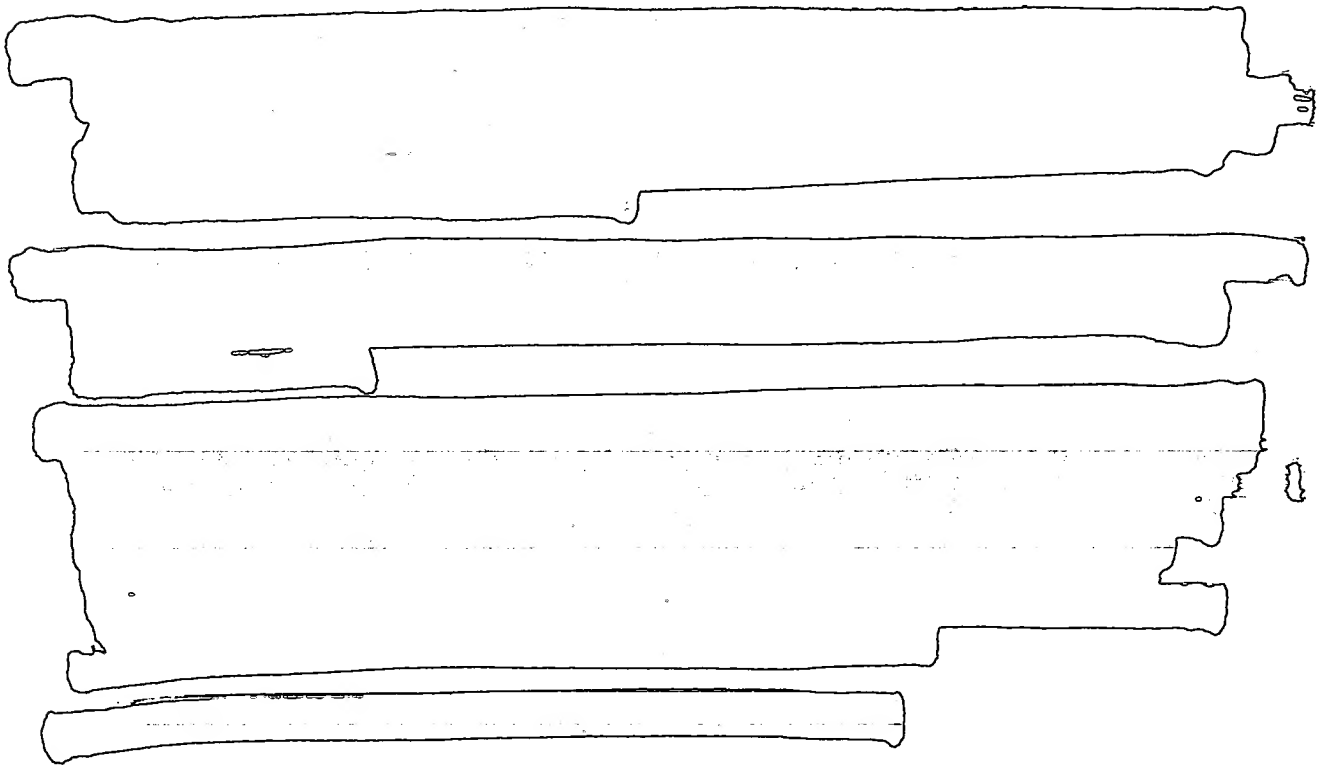
1. Warner-Lambert would provide a commitment letter to the FDA, stating that the 5-week dog study would be initiated promptly and completed within a reasonable period of time. (This letter was received June 18, 1987.) A draft protocol for this study was provided at the meeting, and reviewed and approved by Dr. Norma Browder, and your company so notified on June 18, 1987.

2. It was agreed that additional studies in dogs at higher doses would be undertaken to parallel Phase III clinical studies at higher doses in humans. It is understood that clinical studies at other trimetrexate doses (e.g. 45 or 60 mg/M^2) will be initiated in the near future. Also, if you plan to clinically test TMTX in combination with leucovorin plus sulfamethoxazole, preclinical toxicity information using this combination will need to be submitted.

[redacted]



4. The proposed Phase III study may proceed following a submission of notification that the vascular accesses have been implanted in all 24 dogs and the deficiencies in the May 27, 1987, letter have been addressed to our satisfaction. You may continue the preparations for this Phase III study but may not enroll patients until you are formally notified to proceed.



[redacted]

[redacted]

17. The 1-AA designation is meant to identify a drug which is reviewed expeditiously by the FDA while an Orphan Drug designation grants exclusivity and tax incentives. Neither of these designations mean that the standards for drug development are categorically different from our customary requirements for logical, progressive accrual of meaningful data capable of demonstrating the potential efficacy and toxicity of the drug. In many respects, drugs being developed as 1-AA, because of their potential benefit to AIDS patients and Orphan Drugs which have a limited population of patients, should be developed in the clearest, most efficient manner possible. The FDA determines which studies constitute adequate "proof-of-efficacy" studies, and which compilations of data or information are acceptable.

18. Pilot studies do not generally provide "substantial evidence" of efficacy on which approval decisions for NDAs can be based. Adequate and well-controlled studies are required for such decisions.

Submit additional information in triplicate and identify with IND 29,796.

Sincerely yours,

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

J. Bora

9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 30,006

Maureen W. Myers, Ph.D.
AIDS Treatment and Evaluation Units
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, MD 20892

OCT -7 1987

Dear Dr. Myers:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug Application (IND) submitted for Trimetrexate (TMTX) and to the submissions dated April 24, July 31, August 7, and August 28, 1987. Please also refer to the meeting between this Division, Warner-Lambert, National Institute of Allergy and Infectious Diseases (NIAID), and National Cancer Institute (NCI) representatives on June 17, 1987.

We have completed our review of these submissions and find the study may proceed. However, please revise the consent form to state the following:

[redacted]

The Phase III study of 45 mg/M^2 TMTX may proceed based on our receipt of the August 28, 1987 letter from Warner-Lambert providing formal notification to us that the vascular access ports have been implanted into the 24 dogs for the 5-week toxicity study as agreed at the June 17, 1987 meeting. We acknowledge that dosing in the dogs was to begin September 8, 1987 and be completed by October 16, 1987.

We would like to inform you that since there exist three INDs for the study of TMTX (IND 27,505-National Cancer Institute, IND 29,796-Warner-Lambert, IND 30,006-NIAID), and the studies are not independent projects, in the future we will send all three sponsors of these INDs copies of official correspondence to facilitate communication.

Submit additional information in triplicate and identify with IND 30,006.

Sincerely yours,

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
ORIG. IND 30,006 10/26/87
HFN-815
HFN-815/CSO/JBona/9/1/87/sd/9/23/87 10/5/87
HFN-815/MO/RAlbrecht
HFN-815/CHEM/JTaylor
HFN-815/PHARM/NJBrowder
R/D init. by: ETabor/10/1/87
F/D: 9/24/87/10/5/87
F/T: 9/24/87/10/5/87
1029u

IND FILE COPY

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VARNER LAMBERT

Memorandum

Memo to: Trimetrexate (CI-898) IND 23,269 File
Location: Ann Arbor

Date: September 2, 1987

From: T. N. T. Olson
Location: Ann Arbor

Subject: Phone Call From Mr. James D. Bona (301/443-6797) Regarding the Clinical Hold on the Clinical Study with Trimetrexate for Pneumocystis.

Mr. Bona in response to my phone call of September 1, 1987, phoned at 9:30 on September 2, 1987 to inform me that he had just spoken with Dr. Tabor and that the clinical hold had been lifted. He said that he was preparing a letter to us and that we should receive it within a week (or so).

I also informed him that NIAID would be submitting for their approval a Treatment IND within the next week. He said that Dr. Tabor had spoken with Dr. Bruce Chabner the previous day about that IND. Dr. Chabner had informed Dr. Tabor that IRBs were refusing to take part in the Treatment IND because of the clinical hold imposed on the large NIH clinical study. Mr. Bona indicated that with the clinical hold lifted NIAID would now be permitted to obtain approval of the Treatment IND.

I next raised the subject of the recently completed NIAID clinical studies being used as the second required clinical study for the NDA. I stated that just because it was a Phase 1 or 2 study did not preclud it from being a pivotal NDA study as insinuated by Dr. Albrecht. He agreed that under certain conditions that such a study could be utilized as the second study. I requested that if the results of the soon to be initiated NIH study were good, would he discuss the use of the completed study as one of the two studies with Dr. Tabor. He agreed to have this discussion with Dr. Tabor at an appropriate time and acknowledged that some kind of NDA approval would be politically necessary if the second NIH study results were profound.

Next I questioned him about the number of patients that would be necessary for proof of safety in such an NDA. I indicated that it looked like about 200 patients on trimetrexate would be available for such an NDA and would that be sufficient. I suggested that if it were not, then the patients being entered into the Treatment IND would become very important. I described to him the requirement of 1000 patients of the Cardio-Renal Division and the fact that we had a proposed NDA turned down because it only had 500 patients in it. He said that his Division did not have such a requirement, at least one that he was aware of, and that he would also discuss that with Dr. Tabor.

T. N. T. Olson

cc Dr. J. Bender
Dr. F. Kapp
Mr. C. Lents
Dr. D. Maxwell
Mr. J. Meisenhelder

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

//

IND 29,796

Travis Olson, Ph.D.
Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106

OCT 21 1987

Dear Dr. Olson:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted for trimetrexate (TMTX) and to your submissions dated July 8, 1987 and August 28, 1987. Please also refer to the telephone conversations between Dr. Renata Albrecht and you on July 21, 1987 and Dr. Albrecht and David Pegg on August 14, 1987 and the meeting between this Division, Warner-Lambert, National Institute of Allergy and Infectious Diseases (NIAID), and National Cancer Institute (NCI) representatives on June 17, 1987.

This is to confirm the agreements reached via telephone on August 14, 1987 regarding changes in the animal toxicity studies for TMTX and leucovorin. The 5-week toxicity study will consist of the following study design as outlined in your letter of August 28, 1987:

[redacted]

The Phase III study of 45 mg/M^2 TMTX may proceed based on our receipt of your August 28, 1987 letter providing formal notification to us that the vascular access ports have been implanted into the 24 dogs for the 5-week toxicity study as was agreed at the June 17, 1987 meeting. We acknowledge that dosing was to begin September 8, 1987, and be completed by October 16, 1987.

Since there are three INDs for the study of TMTX (IND 27,505-National Cancer Institute; IND 29,796-Warner-Lambert; IND 30,006-NIAID), and they are not independent projects, in the future we will send all three sponsors copies of pertinent official correspondence.

Submit any further additional information in triplicate and identify with IND 29,796.

Sincerely yours,

E. Tabor

Edward Tabor, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

US BIOSCIENCE

Barbara Scheffler

Senior Vice President
Clinical Operations and Regulatory Affairs

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February 1, 1993

via Federal Express

David Feigal, M.D.
Division Director
Division of Anti-Viral Drug Products
Food and Drug Administration
5600 Fishers Lane
HFD-530
Rockville, MD 20857

RE: NDA #20-326
Neutrexin™ I.V.
Infusion (trimetrexate)

This Submission: New Drug Application (NDA)

Dear Dr. Feigal:

Enclosed please find two copies (1 archival, 1 review copy) of U.S. Bioscience's New Drug Application for Neutrexin™ I.V. Infusion (trimetrexate). As per our conference call with Dr. Mark Goldberger on January 11, 1993, the proposed indication for Neutrexin™ I.V. is as follows:

> *Neutrexin™ I.V. Infusion (trimetrexate) with concurrent leucovorin administration (leucovorin protection) is indicated as an alternative therapy for the treatment of moderate or severe Pneumocystis carinii pneumonia in patients with acquired immunodeficiency syndrome (AIDS) who are not candidates for trimethoprim/sulfamethoxazole therapy.*

This submission consists of 109 volumes. Four additional copies of the draft labeling are appended to this letter. The summaries have been transferred to disks using WordPerfect 5.1 and will be sent directly to Mr. Isom.

In preparing this application, U.S. Bioscience has addressed all the issues discussed with the Division of Anti-Viral Drug Products at our meetings of [redacted]. Analyses requested by the FDA in their letter of March 11, 1992 have been incorporated into the Integrated Clinical and Statistical Reports. [redacted]

One Tower Bridge
100 Front Street • West Conshohocken, PA 19428
(215) 832-4505 • FAX (215) 832-4500

We appreciate the guidance the Division has provided and look forward to working together to expeditiously address any questions that arise during your review. Please contact me if I can be of any assistance. My office telephone number is (215) 832-4505 and my telefax is (215) 832-4500.

Sincerely,

Barbara Scheffler

Barbara Scheffler

Enclosures

cc: [redacted]

ta/129TMTX.NDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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RECEIVED
FEB 0 8 1993
B. J. SCHEFFLER

FEB 4 1993

NDA NUMBER 20-326

Barbara Scheffler
Senior Vice President
Clinical Operations &
Regulatory Affairs
U.S. BIOSCIENCE, Inc.
One Tower Bridge
100 Front Street, Suite 400
P.O. Box 851
West Conshohocken, PA 19428

Dear Ms. Scheffler:

WE HAVE RECEIVED YOUR NEW DRUG APPLICATION (NDA) SUBMITTED PURSUANT TO SECTION 505(B)/507 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT FOR THE FOLLOWING:

NAME OF THE DRUG: **Neutrexin (trimetrexate) I.V. Infusion**

DATE OF THE APPLICATION: **February 01, 1993**

DATE OF RECEIPT: **February 01, 1993**

OUR REFERENCE NUMBER: **20-326**

UNLESS WE FIND THE APPLICATION NOT ACCEPTABLE FOR FILING, THE FILE DATE WILL BE **APRIL 02, 1993**. PLEASE BEGIN ANY COMMUNICATIONS CONCERNING THIS APPLICATION BY CITING THE NDA NUMBER LISTED ABOVE AND ADDRESS AS FOLLOWS:

DAVID ISOM
CONSUMER SAFETY OFFICER
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH, HFD-530
ATTENTION: DOCUMENT CONTROL ROOM
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857
(301) 443-9553

SINCERELY YOURS,

D J C. Isom

CONSUMER SAFETY OFFICER
DIVISION OF ANTIVIRAL DRUG PRODUCTS
CENTER FOR DRUG EVALUATION AND RESEARCH